GENERAL PATHOLOGY AND PATHOLOGICAL PHYSIOLOGY

Behavioral Effects of Para-Chlorophenylalanine in Gonadectomized Male Rats

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Para-chlorophenylalanine restores impaired conditioning and retention of active avoidance reaction in castrated animals and improved their behavior in the open field test.

Key Words: *gonadectomy; para-chlorophenylalanine; training; behavior*

Androgen deficiency impairs the realization of active training process and essentially modified animal behavior in the open field test [6]. Studies of the content of various of neurotransmitters in brain structures after gonadectomy (GE) revealed no clear-cut relationships between training efficiency and the levels of neurotransmitters, their metabolites, or turnover [8]. The most pronounced shifts (although not always significant) were observed in the dopaminergic and serotoninergic systems. Of particular interest are possible corrective effects of various neurotropic agents affecting these neurotransmitter systems on training and behavior in animals with androgen imbalance. Our present studies are devoted to behavioral effects of drugs affecting the serotoninergic system under conditions of androgen imbalance, since serotoninergic system is involved into the mechanisms of learning and memory and in the regulation of endocrine functions [1,3].

Here we evaluated the effects of para-chlorophenylalanine (p-CPA) on learning and behavior in castrated male rats.

MATERIALS AND METHODS

The study was carried out on random-bred adult male albino rats (180-200 g) from Rappolovo breeding center. The animals were kept under standard vivarium conditions with natural illumination and free access to water and food. The experiments were carried out from 10:00 to 13:00. Intact males (n=10) served as the control. Twenty animals were gonadectomied. Ten of these were intraperitoneally injected with p-CPA (300 mg/kg, Sigma) 48 h before behavioral tests. This treatment reduced serotonin level by 60-80%. According to published data, this effect of p-CPA persists for 7 days [5], and therefore after 6 days of the experiment the animals received an additional dose of this substance.

Learning ability was studied on the model of conditioned active avoidance reflex (CAAR) [2] and behavior was studied in an open field [4].

The results were processed using Student t test and Statgraphics software.

RESULTS

In GE rats injected with p-CPA, the first correct response to the conditioned stimulus was recorded on day 1 of training, similarly as in the control (Fig. 1). By day 5 of the experiment the number of correct responses in castrated males treated with p-CPA was 6.0±0.2, which significantly surpassed that in GE rats (3.3±0.3, p<0.001) and was virtually the same as in intact rats (6.2±0.2).

On day 8 of the experiment (after period of learning without electrical stimulation) the reproduction of

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CAAR in GE males treated with p-CPA was 5.0±0.4 correct responses, while in castrated males not treated with p-CPA no correct responses were recorded. By day 12 the number of correct avoidance responses in castrated males treated with p-CPA was 1.0±0.2, which corresponded to CAAR extinction in the control group.

Injection of p-CPA to GE males leveled the effect of testosterone deficiency on behavioral reactions in the open field test (Table 1). The total motor activity returned to the control values, the number of grooming and defecation acts increased in comparison with those in GE rats.

Hence, the decrease in brain serotonin content after injection of p-CPA had a positive impact on learning under conditions of androgen deficiency and improves acquisition and reproduction of CAAR. The observed changes in behavioral reactions in the open field test in animals with androgen deficiency correlated with improvement of active learning. According to published data, androgen deficiency impairs active and passive learning and leads to spontaneous loss of memory and changes in animal behavior [9]. Injection of testenate (25 mg/kg) increased testosterone level in the blood of castrated males, which was paralleled by essential improvement of memory but not normalization of behavioral reactions [9]. In our experiments p-CPA normalized conditioned responses and structure of behavior in GE animals.

Serotonin is involved in the realization of higher nervous activity and regulation of endocrine glands [3,7,10]. Adequate consolidation of time relationships requires an optimal level of serotonin in the brain, while decrease or, more so, increase of these concentrations deteriorates consolidation of temporal relationships in the brain leading to partial or complete amnesia [1,10,11]. Presumably, the effect of serotonin on the higher nervous activity is realized mainly at the cerebral level and through the pituitary (modulation of the secretion of tropic hormones) [3,5]. Injection of p-CPA leads to long-term exhaustion of neuronal serotonin depots in the brain, which is paralleled by a decrease of tissue catecholamine level, though less

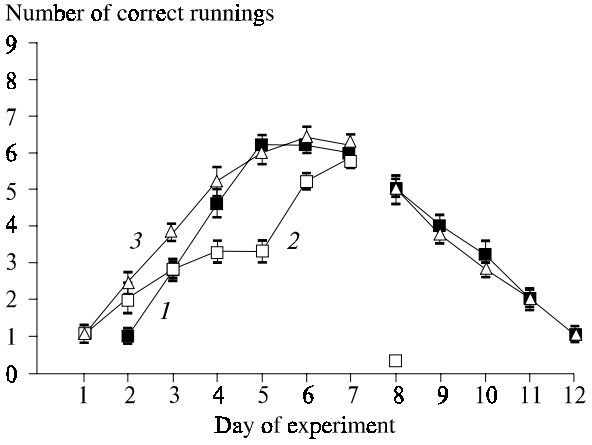

Fig. 1. Effect of para-chlorophenylalanine (p-CPA) on acquisition and extinction of active avoidance response in gonadectomied male rats. *1*) intact rats; *2*) gonadectomy; *3*) gonadectomy+p-CPA.

pronounced [7,11]. On the other hand, GE decreases of the content of testosterone and increased secretion of gonadotropin. Moreover, changes in the serotonin concentrations in cerebral structures were shown to affect the level of gonadotropin in the body [3]. Behavioral changes observed after injection of p-CPA to GE males in our experiments can be due to the fact that this agent provides serotonin level needed for adequate conditioned reflex activity and/or decreases gonadotropin secretion, *i.e.* acts as a modulator. This apparently promotes balanced physiological processes in both the neurotransmitter and hormonal systems. However these hypotheses are to be verified in further studies with selective agonists and antagonists of serotonin receptors. Our results prompt further investigation of drugs affecting the serotoninergic system as potential agents for correction of nervous disorders accompanying endocrine diseases involving changes in androgen concentrations.

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TABLE 1. Effect of p-CPA on Behavior of Gonadectomied Male Rats in Open Field Test during 180 sec (*M*±*m*, *n*=10)

Parameter		Control	GE	GE+p-CPA
Motor activity	number of crossed squares	52.7±6.9	53.2±5.2	57.2±6.5
	number of rearings	14.2±3.2	29.0±3.4**	21.0±4.2
Exploratory activity, arb. units		3.0±0.5	6.2±0.8**	9.0±2.8*
Number of grooming reactions		3.2±0.4	0.6±0.1*	3.0±0.1^{+}
Number of defecations		2.4±0.2	0.9±0.1*	3.0±0.2^{+}

Note. $p<0.001$: **vs.* the control, $^{+}$*vs.* GE; **$p<0.05$ *vs.* the control.

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